



US009636427B2

(12) **United States Patent**
Meyer et al.

(10) **Patent No.:** **US 9,636,427 B2**
(45) **Date of Patent:** **May 2, 2017**

(54) **PROCESS FOR PREPARING A
PHARMACEUTICAL FORMULATION OF
CONTRAST AGENTS**

7,385,041 B2 6/2008 Chang et al.
2003/0059368 A1 3/2003 Groman et al.
2004/0170566 A1 9/2004 Chang et al.

(71) Applicant: **GUERBET**, Villepinte (FR)

FOREIGN PATENT DOCUMENTS

(72) Inventors: **Dominique Meyer**, La Rochelle (FR);
Claire Corot, Lyons (FR); **Marc Port**,
Deuil la Barre (FR); **Vincent Barbotin**,
Montmorency (FR); **Bruno**
Bonnemain, Villeparisis (FR)

EP 0 270 483 A2 6/1988
EP 0 481 526 A1 4/1992
EP 0 454 078 B1 10/1996
FR 2 590 484 A1 5/1987
JP 4-504436 A 2/1992
JP 4-504436 A 8/1992
JP 2005-534697 A 11/2005
WO WO 86/02352 A1 4/1986

(73) Assignee: **GUERBET**, Villepinte (FR)

(Continued)

(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

OTHER PUBLICATIONS

(21) Appl. No.: **15/140,077**

(22) Filed: **Apr. 27, 2016**

(65) **Prior Publication Data**

US 2016/0235867 A1 Aug. 18, 2016

Related U.S. Application Data

(63) Continuation of application No. 12/918,259, filed as
application No. PCT/EP2009/051937 on Feb. 18,
2009, which is a continuation of application No.
12/155,997, filed on Jun. 12, 2008, now abandoned.

(30) **Foreign Application Priority Data**

Feb. 19, 2008 (FR) 08 51055
Apr. 17, 2008 (EP) 08154745

(51) **Int. Cl.**

A61K 49/10 (2006.01)
A61K 45/06 (2006.01)
A61K 9/00 (2006.01)

(52) **U.S. Cl.**

CPC **A61K 49/108** (2013.01); **A61K 9/0019**
(2013.01); **A61K 45/06** (2013.01); **A61K**
49/106 (2013.01)

(58) **Field of Classification Search**

None
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,639,365 A 1/1987 Sherry
4,647,447 A 3/1987 Gries et al.
4,877,600 A 10/1989 Bonnemain et al.
5,049,667 A 9/1991 Schaefer et al.
5,082,649 A 1/1992 VanDeripe
5,098,692 A 3/1992 Gries et al.
5,362,475 A 11/1994 Gries et al.
5,364,613 A 11/1994 Sieving et al.
5,650,133 A 7/1997 Carvalho et al.
5,846,517 A 12/1998 Unger
5,876,695 A 3/1999 Gries et al.
5,958,373 A 9/1999 Garrity et al.

“A Guideline on Summary of Product Characteristics (SmPC)”,
Revision 2, Sep. 2009.

“Excipients in the label and package leaflet of medicinal products
for human use”, vol. 3B, Guidelines: Medicinal products for human
use safety, environment and information, Jul. 2003.

“MRI Contrast Agent”, Pharmacia, vol. 37, No. 5, 2001, pp.
420-421 with English language translation.

“Nephrogenic Systemic Fibrosis: an Uncommon and Debilitating
Disease Possibly Associated with Gadolinium Chelates”, Guerbet
Contrast for Life, Information for Healthcare Professionals and
Investors, (online), Dec. 21, 2007, pp. 1-7, XP002499276.

“Nephrogenic Systemic Fibrosis: An uncommon and Debilitating
Disease Possibly Associated with Gadolinium Chelates”, Informa-
tion for Healthcare Professionals and other Stakeholders, dated Jul.
2, 2008.

“Stability of linear and macrocyclic gadolinium based contrast
agents”, The British Journal of Radiology, vol. 80, pp. 581-585,
2007.

(Continued)

Primary Examiner — Nissa Westerberg

(74) *Attorney, Agent, or Firm* — Birch, Stewart, Kolasch
& Birch, LLP

(57) **ABSTRACT**

The invention relates to a process for preparing a liquid
pharmaceutical formulation containing a complex of mac-
rocyclic chelate with a lanthanide and a mol/mol amount of
free macrocyclic chelate of between 0.002% and 0.4%,
advantageously between 0.02% and 0.3% and very advan-
tageously between 0.025% and 0.25%, the macrocyclic
chelate advantageously being chosen from DOTA, NOTA,
DOTAGA, DO3A, BT-DO3A, HP-DO3A and PCTA, and is
preferably DOTA, the said process comprising the following
successive steps: b) preparation of a liquid pharmaceutical
composition containing, firstly, the complex of macrocyclic
chelate with a lanthanide, and, secondly, free macrocyclic
chelate and/or free lanthanide; c) measurement in the phar-
maceutical formulation obtained in step b) of the concen-
tration of free macrocyclic chelate C_{ch1} and/or of free
lanthanide C_{lan1} ; d) adjustment of C_{ch1} and/or of C_{lan1} so as
to obtain $C_{ch1}=C_{tch1}$ and $C_{lan1}=0$, wherein C_{tch1} is the target
concentration of free macrocyclic chelate in the final liquid
pharmaceutical formulation.

20 Claims, No Drawings